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10/510,015

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EXAMINER

STOICA, ELLY GERALD

ART UNIT

PAPER NUMBER

1647

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
|------------------------------|---------------------------------------|---|--|
| Office Action Summary | Application No. 10/510,015 | Applicant(s) SOTO-JARA ET AL. | |
| | Examiner ELLY-GERALD STOICA | Art Unit 1647 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01/17/2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 35-37,39 and 57-94 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 35-37,39 and 57-94 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the claims

1. In the remarks submitted on 01/17/2008 Applicants have canceled claims 38, 47, 51 and 56, amended claims 35 and 39 and added new claims 57-94. Accordingly, claims 35-37, 39 and 57-94 are currently examined.

Withdrawn claim rejections

2. The rejections under 35 USC § 102 (b) of the claims:

- 35-39 and 47 over Godfrey et al. (U.S. Pat. 6,242,566);
- 35-36 over O'Hare et al. (U.S. Pat. No.: 6,017,735);
- 35 and 39 over Godfrey et al. (J. Exp. Med. 180, 757-762, 1994);
- 35, 36 and 47 over Weinberg et al. (U.S. Pat. 6, 312, 700);

are withdrawn in view of the amendment to the claims.

Maintained and New claim rejections necessitated by amendment

Claim Rejections - 35 USC § 112

3. Claims 35-37, 39 remain and the claims 57-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the claims encompass an isolated polypeptide consisting of or a composition comprising an

isolated polypeptide or a composition of matter comprising a solid support and an isolated polypeptide consisting of :

- a) amino acids 94-124 of human OX40 ligand (OX40L) ;
- b) a peptide sequence of OX40L of between 5 and 10 amino acids that binds to OX40R;
- c) an active mutant of a) or b) wherein one or more of the amino acids has been conservatively substituted and said active mutant binds to OX40R;

Also claimed is an isolated peptide designed on the sequence, the structure or the sequence and structure of an amino acid sequence corresponding to 107-116 (SEQ NO ID: 8) or 107-111 (SEQ ID NO: 13) of human OX40L.

Thus, the claims are drawn to a genus of peptides that are defined by their functionality. The sequence defined by Sequence Id. Nos.: 6, 8 and 13 also provide structural limitations. The above sequences claimed (i.e., a peptide sequence between 5 and 10 amino acids that binds to OX40R, an active mutant or fusion proteins or derivatives containing them) do not have adequate written description.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is the functionality of the claimed peptides. With the exception of the peptides having Seq. Id.

Nos.: 6, 8 and 13 there is no identification of any particular portion of the structure that must be conserved and linked to the functionality of the peptide. There is no requirement for the peptides of 5 to 10 amino acids with regard to the structure or the region of the protein that they are part of apart for the description of the Seq. Id. Nos.: 6, 8 and 13 or even if they are part of a human protein. The recitation of amino acid numbers absent an identified sequence (by Seq. Id. No.) does not provide an adequate written description. The sequence numbering is not inherent to the protein. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*” (See page 1117). The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed” (See *Vas-Cath* at page 1116).

Therefore, only the peptides having the Seq. Id. Nos.: 6, 8 and 13 but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

In the remarks submitted 01/17/2008, Applicant argued that the claims are adequately described for all the claims breadth and also amended the claim by

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eliminating the Seq. Id. No. for the sequences that were adequately described and broadened the claim by amending the OX 40L not to recite human OX40L. This was not found persuasive because, as iterated supra, adequate written description is conferred by the correlation between structure and function and, as amended, the claims are even further from the situation *ante*.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 35-37, 39 remain and claims 57-94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically part e) of the independent claims 35, 69 and 82 it is unclear if the recitation "one or more" may include the situation in which all the amino acids may be substituted. For part g) of the above mentioned claims it is unclear what the metes and bounds of "a derivative" are. Moreover for parts b), c), f)ii), f)iii) it is unclear if the OX40L or the OX40R are human protein or not, since they are not identified by a Seq. Id. No. Thus the metes and bounds of the claims could not be determined.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

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the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 35-37, 39 and 57-94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Godfrey et al. (U.S. Pat. 6,242,566) in view of Chien et al. (Proc. Natl. Acad. Sci. USA, 88, 9578-9582, 1991- cited in the prior Office action).

The claims are drawn to an isolated polypeptide consisting of an isolated polypeptide consisting of or a composition comprising an isolated polypeptide or a composition of matter comprising a solid support and an isolated polypeptide consisting of:

- a) amino acids 94-124 of human OX40 ligand (OX40L);
- b) amino acids 94-124 of human OX40L, wherein one or more amino acids have been deleted, said polypeptide binds amino acids 107- 111 of human OX40L and said polypeptide binds to the OX40 receptor (OX40R);
- c) between 5 and 10 contiguous amino acids of OX40L, wherein said polypeptide contains amino acids 107-111 of OX40L and binds to OX40R;
- d) amino acids 107-116 or 107-111 of human OX40L;

e) an active mutant of a), b), c) or d), wherein one or more of the amino acids has been conservatively substituted and said active mutant binds to OX40R;

f) a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to:

i) a peptide consisting of amino acids 94-124 of human OX40L;

ii) a peptide consisting of amino acids 94-124 OX40L, wherein one or more amino acids have been deleted, said peptide contains amino acids 107-111 and said fusion polypeptide binds OX40R;

iii) a peptide sequence of human OXd0L an amino acid sequence of between 5 and 10 contiguous amino acids of OX40L that includes amino acids 107-111 of OX40L and said fusion polypeptide binds to OX40R;

iv) a peptide consisting of amino acids 107-116 or 107- 111 of human OX40L;

or g) a derivative of a), b), c), d), e) or f).

Godfrey et al. teach purified ACT-4-L (which is an earlier name for OX40L- as acknowledged by Applicant) ligand polypeptides; an exemplified ACT-4-L ligand designated ACT-4-L-h-1. The polypeptide of Seq. Id. No.: 6 of the instant Application is 100% identical with the amino acid string 94-124 of the Seq. Id. No.: 4 of Godfrey et al. (result presented in the prior Office action)

Godfrey et al. also teach purified extracellular domains of ACT-4-L ligands. the sequence 51-183 of the OX40L is presented as being the extracellular region of the protein and, by inference, the portion of the polypeptide implicated in the binding to the

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OX 40- its receptor. The purified extracellular domains taught by Godfrey et al. comprise at least five contiguous amino acids from the full-length ACT-4-L-h-1 extracellular domain. Some extracellular domains consist essentially of a domain possessing a particular functional property, for example, the capacity to specifically bind to the ACT-4-h-1 receptor expressed on the surface of CD4⁺ T-cells. Any of the above extracellular domains may further comprise a linked second polypeptide such as the constant region of an immunoglobulin heavy chain (col. 2, line 46 to col. 3, line 5). Also described by Godfrey et al. are ligands representing allelic, nonallelic, splice and higher cognate variants of ACT-4-L-h-1, and natural or induced mutants of any of these. Such variants will typically show substantial sequence identity with the ACT-4-L-h-1 sequence, and contain at least 4 and more commonly 5, 6, 7, 10 or 20, 50 or more contiguous amino acids from the ACT-4-L-h-1 sequence (col. 12, lines 15-22). Besides the full-length polypeptides, Godfrey et al. teach biologically active fragments of full-length ACT-4-L ligand polypeptides (synonymous to active mutant of the instant application). Significant biological activities include binding to an ACT-4 receptor such as ACT-4-h-1 and a segment of a full-length ACT-4-L ligand polypeptide will ordinarily comprise at least 5 contiguous amino acids of the ACT-4-L (col.13, lines 21-38). Godfrey et al. also disclose fusion partners for the ACT-4-L polypeptides that include toxins (e.g., diphtheria toxin, Pseudomonas ectotoxin A, ricin toxin or phospholipase C) and immunoglobulin components. The recombinant globulins formed by fusion of ACT-4-L fragments and immunoglobulin components often have most or all of the physiological properties associated with the constant region of the particular immunoglobulin class used (col. 14,

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lines 58-59, col. 10, lines 43-53). The fusion proteins can be used to immobilize the peptide by the way of recombinant globulins, for binding analysis (i.e., solid support) (col. 11, lines 1-3; col.14, lines 64-67; col. 23, lines 1-3). Godfrey et al. also teach that ACT-4-L polypeptides can be synthesized by chemical methods which are well known in the art and necessarily include a solid support for the synthesis of the peptide and are described further by Berger & Kimmel, *Methods in Enzymology*, Volume 152, *Guide to Molecular Cloning Techniques* Academic Press, Inc., San Diego, Calif., 1987) (col. 16, lines 35-42).

Godfrey et al. also teach pharmaceutical compositions containing fragments of the ACT-4-L and suitable pharmaceutical excipients, carrier, stabilizers, etc (col. 24, line 63 to col. 24 line13). Godfrey is silent with respect to the specific sequences (by amino acid positions) that contain the specific domains involved in the specific binding to OX 40 R. It is noted though that once these specific amino acids were identified, it was routine in the art to introduce conservative mutations or delete non essential amino acids and retain the functionality of the domain.

Chien et al teach a method by which a protein-protein interaction is identified in vivo through reconstitution of the activity of a transcriptional activator. The method is based on the properties of the yeast GAL4 protein, which consists of separable domains responsible for DNA-binding and transcriptional activation. Plasmids encoding two hybrid proteins, one consisting of the GAL4DNA-binding domain fused to protein X and the other consisting of the GAL4 activation domain fused to protein Y, are constructed and introduced into yeast. Interaction between proteins X and Y leads to the transcriptional

activation of a reporter gene containing a binding site for GAL4. The utility of this in vivo approach (designated the two-hybrid system) to screen a random library for an interacting protein is presented and the authors also underscore the obviousness of the method for identifying interacting peptides (Introduction, second paragraph).

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to use the methodology of Chien et al. to detect the interacting domains of the ACT-4-L to its receptor with a reasonable expectation of success because the methods used were readily available (as taught by Chien et al., which also suggested the usefulness of the method). The motivation to do so is offered by Godfrey et al. which teaches the uses of the ACT 4 L fragments and their biological use. By employing the methods of Chien et al. A person of ordinary skill in the art would have necessarily arrived to the domains that are essential to the binding of ACT 4 L (i.e., OX 40L) to its receptor because the domain to be searched was disclosed by Godfrey et al. (51-183 of the OX40L) so that the search would have entailed a finite number of fragments, already envisioned (in length) perfectly feasible within the technical grasp of a person of ordinary skill in the art which read the references as a whole.

Conclusion

9. No claims are allowed.
10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

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/Manjunath N. Rao, /
Supervisory Patent Examiner, Art Unit 1647